# Studies on the Pathogenesis of Peptic Ulcers

Experimental Studies

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MAX BERG

B.S., University of Illinois, 1932
M.S., University of Illinois, 1934
M.D., University of Illinois, 1935

## THESIS

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# EXPERIMENTAL PEPTIC ULCERATIONS BY VASOMOTOR EPISODES (PITRESSIN EPISODES) AND AUTONOMIC DISTURBANCES

MAX BERG, M.D., PH.D.
CHICAGO

The extensive literature on the genesis of peptic ulcers presents a number of divergent points of view. Experimentally, interference with the factors on which the vitality of the mucosa is normally dependent, i. e., secretion, circulation and innervation, has given rise to erosions and ulcers, and clinically when peptic ulcers develop it is reasonable to suppose that these factors are affected.

From the literature it appears that local circulatory disturbances produced in various ways are an important factor in initiating peptic ulcers. Disturbed innervation, the neurogenic factor, among others, plays a part not only in the initiation of some of the vascular changes but also in the exacerbations and resulting chronicity of the lesions.

Virchow [1] first laid emphasis on the possible relationship of local circulatory disturbances to peptic ulcer. He noted hemorrhagic necrosis of the mucosa preceding ulceration, which he attributed to vascular spasm. The importance of arteriosclerotic changes in the older age groups has been pointed out by a number of writers. Aschoff [2] expressed the belief that local spasm of the arteries of the stomach is an important factor in the development of erosions, particularly along the gastric pathway.

Anatomically it has been pointed out that the areas in which the greatest number of ulcerations are found have a deficient circulation, i. e., the areas immediately proximal and distal to the pylorus.[3] The arteries of the submucosa in the pyloric region of the inferior portion of the lesser curvature are practically terminal vessels and are sparsely distributed, thus giving a limited blood supply to this area.[4] These arteries are subject to powerful and repeated constrictions by the musculature of the stomach.

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From the Department of Pathology, Bacteriology and Public Health, University of Illinois College of Medicine.

1. Virchow, R.: Virchows Arch. f. path. Anat. **5**:632, 1853.
2. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, 1924.
3. Einhorn, M.: Surg., Gynec. & Obst. **50**:416, 1930.
4. Reeves, T. B.: Surg., Gynec. & Obst. **30**:374, 1920.

The occasional association of an intracranial tumor or an ulcer has been recorded. Experimentally, intracranial lesions have led to ulcerations of the stomach and duodenum. Stimulation of various centers has also led to ulcerations. Stimulation of the sympathetic and of the vagus nerves, too, has been associated with gastric lesions. The general ideas of Eppinger and Hess [5] on vagotonia were fostered by von Bergmann,[6] who directed attention to the anemic patches and subsequent ulcerations that occur on occlusion of the vessels by intense muscle spasm. In later papers, while disclaiming that hypervagotonicity is the cause of all ulcers, he asserted that such lesions are more common in persons with a neuropathic constitution—the asthenic, slender habitus. Robinson and Brucer,[7] in a statistical study on a large group of patients with ulcers, pointed out that a statistically significant association was found between slender habitus and ulcers.

In this study the influence of vascular spasm and relaxation as evoked by pitressin in the presence of disturbed innervation as compared with intact innervation on the production of peptic ulcers was investigated.

Because of the conflicting reports in the literature on gastric motility, it was decided to study also the influence of pitressin on the stomach and duodenum.

## EXPERIMENTAL OBSERVATIONS

For the study of the effect of pitressin on gastric motility, 12 dogs of approximately the same size and weight were chosen. After a period of training they were subjected to repeated fluoroscopic examinations both before and after operation. In 6 dogs the vagus nerves were cut as they emerged through the diaghragm. In the other 6 both the splanchnic and the sympathetic nerve chains were severed through the abdominal approach. The dose of pitressin injected with certain variations was 20 units per 5 kilograms (following the technic of Nedzel [8]). A third group of 6 normal dogs were used as controls.

The reaction to the dose of pitressin just given varied somewhat from time to time in the same animal and from animal to animal.

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5. Eppinger, H., and Hess, L.: Vagotonia, New York, Nervous and Mental Disease Publishing Company, 1915.

6. von Bergmann, G.: München. med. Wchnschr. **60**:169, 1913; Berl. klin. Wchnschr. **50**:2374, 1913; **55**:524, 1918; Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1923, supp. 4, p. 20; Pathologische Physiologie, Berlin, Julius Springer, 1932.

7. Robinson, S. C., and Brucer, M.: Am. J. Digest. Dis. **7**:365, 1940.

8. Nedzel, A. J.: (*a*) Proc. Soc. Exper. Biol. & Med. **34**:150, 1936; (*b*) Arch. Path. **26**:988, 1938.

The initial reaction in all three groups of dogs was dilatation of the stomach with complete cessation of peristaltic activity. This period was shortest for the vagotomized group (average, seven minutes), slightly longer for the normal group (average, eleven minutes) and markedly increased in the sympathectomized group (average, eighteen minutes). In all three groups, following the initial inhibition, a marked increase in the amplitude and the force of peristalsis occurred. It was probably the most severe in the vagotomized dogs, as their stomachs emptied at a slightly faster rate than the stomachs of normal dogs. In the sympathectomized dogs the augmentation was considerably diminished as compared with that in the other two groups.

In order to determine whether the immediate cessation of peristaltic movements following the injection of pitressin might not be due to excitement, injections of equivalent amounts of saline solution were made. These failed to produce observable changes in peristalsis. With the injection of minute doses of pitressin, from 0.01 to 0.15 cc. (0.2 to 3 units), only inhibition of peristalsis occurred, lasting four to seven minutes, without subsequent increase in peristaltic movements.

Following the intravenous injection of pitressin, a marked spasm of the mucosal vessels (blanching) occurred, which was followed by vascular dilatation of a rather marked degree; then in scattered areas superficial erosions and edema appeared. The experimentally induced disturbance in innervation showed no appreciable effect on the reaction, with the exception that in the sympathectomized dogs the gastric reaction was less severe and erosions following the injections were more infrequently seen. The gross and microscopic observations in the normal dogs were similar to those reported by Nedzel [8] and Metz and Lackey.[9]

The results of repeated injections of pitressin were studied on three groups of dogs. The dogs were approximately of the same size and weight. Dodds and co-workers [10] reported ulcerations in rabbits, cats, monkeys, guinea pigs, rats and mice following injections of an acetone-trinitrophenol extract of the posterior lobe. Nedzel [8b] reported ulcerations of the stomach in normal dogs following injections of pitressin, and Berg [11] reported ulcerations in vagotomized dogs.

In the first group (12 dogs) pitressin was injected intravenously twice weekly. Because preliminary experiments indicated that more than a few injections were required to produce more than a transient erosion, multiple injections were given to produce lesions of greater extent and chronicity. The animals received from eight to twenty injections. In 3 of the 12 animals, erosions and ulcerations were

9. Metz, M. H., and Lackey, R. W.: Texas State J. Med. **32**:589, 1937.

10. Dodds, E. C.; Noble, S. L., and Williams, P. C.: Lancet **1**:1099, 1935.

11. Berg, M.: Am. J. Digest. Dis. **7**:78, 1940.

found. They were mostly superficial and were usually in the pyloric or the fundic portion of the stomach (table 1). Microscopically, they were similar to equal-sized ulcers seen in the vagotomized animals and will be described in detail later.

The second group consisted of 26 dogs of approximately the same size and weight. The vagus nerves were cut as they emerged through the diaphragm, and the operative results were checked at autopsy.

Beginning two weeks after operation, 20 animals were given from two to fifty injections at the rate of two a week (see table 2).

These animals were killed in from thirty to one hundred and fifty days after the onset of the injections. In 13 of the 20 animals erosions and ulcers were found.

TABLE 1.—*Normal Dogs Given Injections of Pitressin*

| Dog | Injections | Time | Reactions to Injections | Results |
|---|---|---|---|---|
| 1 | 8 | 30 days | Moderate | No gross changes |
| 2 | 8 | 30 days | Moderate | No gross changes |
| 3 | 12 | 40 days | Severe | Two small ulcers |
| 4 | 12 | 40 days | Moderate | Four hemorrhagic erosions near lesser curvature and in pylorus |
| 5 | 12 | 40 days | Moderate | No gross changes |
| 6 | 12 | 45 days | Moderate | No gross changes |
| 7 | 16 | 60 days | Moderate | Numerous small hemorrhagic lesions in pyloric region |
| 8 | 16 | 60 days | Moderate | No gross changes |
| 9 | 16 | 60 days | Moderate | No gross changes |
| 10 | 18 | 60 days | Moderate | Five small ulcerations in stomach in pyloric region |
| 11 | 20 | 70 days | Moderate | No gross changes |
| 12 | 20 | 70 days | Moderate | No gross changes |

Eight injections given over a period of a month were found to produce ulcers in 5 of 6 dogs. In 5 of the dogs the ulcers appeared either in the pyloric region or in the lower portion of the fundus.

Four dogs were killed after receiving ten injections over a period of forty days. They had from five to seven ulcers, all located in the pyloric and the isthmic region of the stomach. The ulcers were larger and deeper than in the previous group.

Eight dogs were killed after receiving fourteen to fifty injections of pitressin and from forty to one hundred and fifty days after the onset of the injections. They were in good health and well nourished with the exception of dog 14, which showed a superficial gastric erosion, and dog 19, which showed hemorrhagic duodenitis; no gross changes were seen in the other animals.

The gross appearance of the earlier lesions may be seen in figure 1. *A* is from dog 5, which was killed after thirty-three days. The lesions are concentrated chiefly along the lesser curvature. In *B* the hemorrhagic duodenitis may be seen.

TABLE 2.—*Vagotomized Dogs Given Injections of Pitressin*

| Dog | Injections | Time | Reactions to Injections | Results |
|---|---|---|---|---|
| 1 | 2 | 8 days | Very severe | Numerous pinhead to pinpoint size hemorrhagic erosions in pyloric portion of stomach extending up to 5 cm. from sphincter |
| 2 | 8 | 30 days | Moderate | No gross changes in stomach or duodenum |
| 3 | 8 | 33 days | Moderate | Two small ulcers in isthmus area near lesser curvature and five small hemorrhagic erosions |
| 4 | 8 | 33 days | Marked | Small ulcer 1 cm. by 0.5 cm. in a hemorrhagic area near lesser curvature 4 cm. from sphincter; four small erosions in fundus of stomach |
| 5 | 9 | 33 days | Moderate | Six small hemorrhagic ulcers in stomach fundus |
| 6 | 10 | 40 days | Moderate | Five definite ulcers in pyloric region and fundus |
| 7 | 10 | 40 days | Severe | Six definite ulcers in pyloric region and fundus |
| 8 | 15 | 50 days | Moderate | No gross changes |
| 9 | 8 | 30 days | Moderate | Six hemorrhagic erosions in stomach |
| 10 | 15 | 78 days | Moderate | No gross changes |
| 11 | 10 | 40 days | Moderate | Four ulcers in pyloric region and three small ones in isthmic region |
| 12 | 14 | 65 days | Moderate | No gross changes |
| 13 | 10 | 35 days | Severe | Numerous pinpoint to pinhead size erosions in pyloric region of stomach and one larger ulcer |
| 14 | 25 | 90 days | Moderate | Small superficial erosion 8 cm. from pyloric sphincter |
| 15 | 25 | 90 days | Moderate | No gross changes in stomach |
| 16 | 4 | 9 days | Severe | Numerous pinpoint to pinhead size hemorrhagic erosions most severe in duodenum and diminishing as it extends down through the jejunum |
| 17 | 16 | 48 days | Moderate | No gross changes |
| 18 | 25 | 90 days | Severe | Hemorrhagic duodenitis with grayish adherent patches |
| 19 | 5 | 16 days | Severe | Severe hemorrhagic duodenitis and jejunitis as described above |
| 20 | 50 | 150 days | Moderate | No gross changes |

Acute bloody diarrhea developed in 3 of the animals, and all these died. Two presented almost identical pictures. The intestinal canal was filled with blood, and beginning sharply at the upper end of the duodenum there was marked hemorrhagic duodenitis, which extended down with diminishing severity to the ileum. The third dog presented numerous pinpoint to pinhead–sized hemorrhagic erosions in the pylorus. Of these 3 animals, 1 died of acute hemorrhagic gastritis and 2 of

hemorrhagic enteritis with the greatest involvement in the duodenum. In none of the animals not operated on which were given pitressin did this occur.

The microscopic picture varied. In the superficial acute erosion the mucosa showed evidence of acute congestion, with dilated vessels filled with blood. At the base and the sides of the erosion, small hemorrhages were found. The destruction of the tissues extended to the muscularis mucosae. On the other hand, in other erosions the vascular changes were not so marked. The erosions were found in local areas of edema, which extended on each side from two to three times the width of the lesion. Near some of these, small lymphocytic accumulations were found.

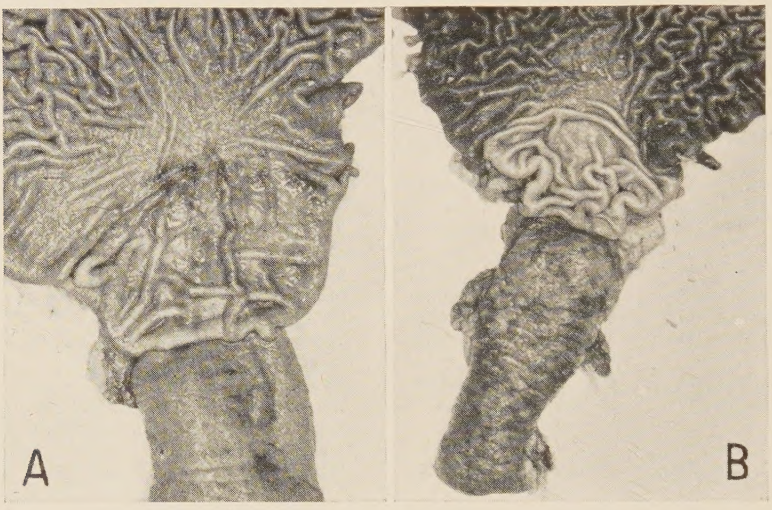


Fig. 1.—*A*, superficial hemorrhagic gastric erosions particularly along the lesser curvature in a vagotomized dog (6) following injections of pitressin. *B*, acute duodenitis with superficial hemorrhagic erosions in vagotomized dog (18) following repeated injections of pitressin.

The deeper ulcers extended down through the submucosa into the muscularis. At the base there was an increase in fibrous tissue, with scattered round cells and scattered dilated vessels; at the margins, fibroblastic proliferation and infiltration by plasma cells. Such an ulcer is shown in figure 2 *A* from dog 6. The lesion extends through the submucosa to the superficial layers of the muscularis. A large thrombosed vessel may be seen to the left.

The microscopic changes in the duodenum were all of an acute nature. The microscopic picture of the acute duodenitis (dog 19) is presented in figure 2 *B*. The many markedly dilated capillaries and

the round cell infiltration near the surface are clearly shown. With slight variations these sections typify the microscopic alterations in the animals presenting duodenitis.

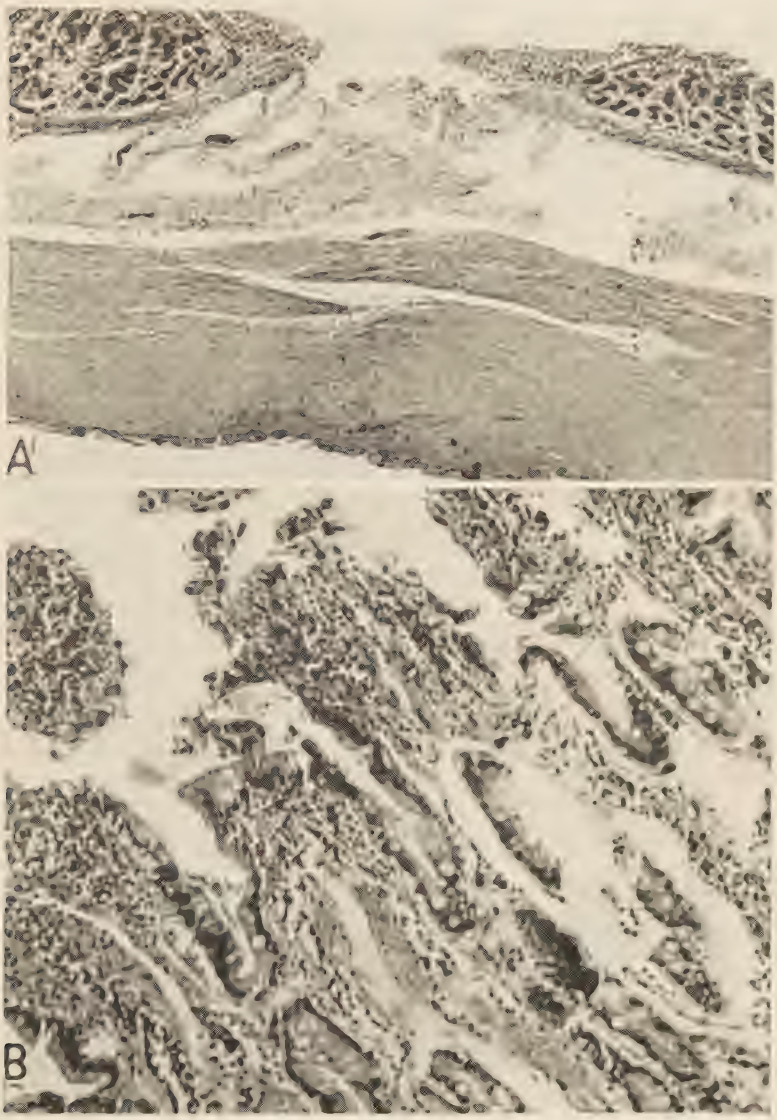


Fig. 2.—*A,* gastric ulcer extending down through the submucosa to the superficial layers of the muscularis, with undermining of the edges by fibroblastic and round cell infiltration. Vagotomized dog 6. × 32. *B,* acute duodenitis showing intense capillary congestion and cellular infiltration. × 110.

In the remaining 6 animals that were vagotomized, but not given pitressin, no evidence of ulceration was found thirty to ninety days

after operation. This confirms the observations of Ivy [12] and others who failed to find evidence of ulceration in vagotomized dogs.

In the third group, consisting of 10 dogs, the splanchnic nerves were sectioned as they came through the diaphragm, many of the fine nerves that enter the adrenals were severed and the sympathetic chain on each side was cut. The operative results were checked at necropsy.

Six dogs were given pitressin in doses as previously described. Three of the dogs were given pitressin twice weekly. Because of the negative results, 2 dogs were given pitressin three times weekly and 1 was given pitressin daily (table 3). In 1 dog a small number of pinpoint hemorrhagic erosions were seen scattered over the first portion of the duodenum. The remaining 4 dogs of this group were used as controls and were not given pitressin. They were killed in from twenty-one to sixty days after operation. In none of this group were lesions demonstrable.

TABLE 3.—*Sympathectomized Dogs Given Injections of Pitressin*

| Dog | Injections | Time | Reactions to Injections | Results |
|---|---|---|---|---|
| 1 | 8 | 30 days | Moderate | No gross changes |
| 2 | 12 | 40 days | Moderate | No gross changes |
| 3 | 18 | 45 days | Severe reaction | No gross changes |
| 4 | 18 | 45 days | Moderate | No gross changes |
| 5 | 18 | 45 days | Severe reaction | A small number of superficial pinpoint hemorrhagic erosions in duodenum |
| 6 | 10 | 10 days | Severe reaction | No gross changes |

In comparing the normal animals that were given injections in the same manner as the vagotomized and sympathectomized groups it was found that ulcerative lesions were produced in 33 per cent of the first group, compared with 61 per cent of the second group, and with 15 per cent (1 dog) of the third group. The animals not operated on required more injections, and the ulcers were usually not as deep or extensive as in the vagotomized group, although in 1 animal a larger ulcer was seen. In the sympathectomized group, the tendency to ulceration was distinctly diminished, and no gastric lesions were observed.

## COMMENT

In the development of the ulcers one notes in both the prepared and the normal groups of animals the initial spasm of the vessels produced by pitressin directly and the spasm produced indirectly as a result of muscular contractions, following which dilatation occurs. In some cases, rupture of a small vessel in the submucosa and superficial erosion occur, or localized areas of edema are found following the ischemia.

12. Ivy, A. C.: Arch. Int. Med. **25**:6, 1920.

These small necrotic areas are digested by the gastric juices, and superficial ulceration may occur. If further spasms do not occur, except as in the particularly reactive animals cited, this lesion heals. With the occurrence of further vascular episodes, the development of ulcers in a certain proportion of the animals follows. The deeper ulcers are similar to those found in man. With the disturbance in innervation from the cutting of the vagus nerves, the ulcers develop more rapidly and more frequently. It appears possible that in the interval between injections the tissues do not recover as rapidly as in the normal dogs, and possibly the spasms are more severe. Aschoff [2] pointed out that ulcers did not heal as rapidly in the vagotomized dogs, and he suggested that the loss of tone of the whole stomach and the decrease in its contractility added considerably to the diminution of the healing tendency. With a disturbance in balance of the vasomotor fibers due to the cutting of the vagus nerves, local spasms [13] leading to impaired vascularity may occur, thus leading to impaired nutrition and diminution of the healing power.

In the sympathectomized dogs the diminished muscular spasm and indirectly the diminished vascular spasm with a resulting lessened tendency to local ischemia and thrombosis may account for the infrequency and the insignificance of the lesions produced.

Long-standing chronic ulcers were not produced. Among the possible factors contributing to this may be mentioned the diminished reaction to pitressin following repeated use, the excellent nutrition of the animals, the gradual resumption of function in the vagotomized animals and what may be cited as the natural tendency for ulcers to heal.

The application of the results of animal experimentation to human pathology is to be ventured only with considerable caution. However, the results may serve to focus attention on certain facts which might otherwise be overlooked or disregarded.

The importance of vascular spasm, not only as produced directly but as caused indirectly, the result of increased muscular constriction, is emphasized by the animal experiments. With disturbed innervation, it is augmented or diminished. Virchow,[1] first, then Aschoff [2] and Smithies [14] (to name but a few of the authors) emphasized the importance of local spasm leading to local anoxia of tissue, predisposing to ulceration and digestion by the pepsin-hydrochloric acid content of the stomach.

It is well recognized that persons subject to ulcers are usually of the asthenic (slender) habitus with labile nervous and vascular systems (Robinson and Brucer [7]). The importance of the vasomotor alterations associated with emotional and anxiety states in aggravating the symptoms of ulcer has been repeatedly emphasized.

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13. Dalla Vedova, R.: Policlin. (supp.) **6**:1153, 1900.
14. Smithies, F.: Am. J. Digest. Dis. **2**:437, 1935.

The disease is often seasonal, and Petersen and Milliken [15] have shown that exacerbations are associated with certain meteorologic alterations (polar and tropical fronts).

In the older patients the problem of ulcer is complicated by arteriosclerotic changes and irregular scarring, the result of repeated inflammatory reactions as a consequence of repeated exacerbations.

While emphasis has been placed on the neurovascular mechanism of peptic ulcer, the importance of the other factors mentioned must not be forgotten.

## SUMMARY

A single injection of pitressin produces vascular contraction and relaxation with scattered superficial erosions or localized areas of edema. These occur with about the same extent and frequency in normal and in vagotomized dogs. In sympathectomized animals, the reaction is diminished, and erosions or localized areas of edema are infrequent.

Injections of pitressin produce, first, inhibition of gastric and duodenal peristalsis. This period of inhibition is shortest in vagotomized dogs and longest in sympathectomized dogs, normal dogs occupying an intermediate position. This is followed by severe gastric peristalsis in the normal and the vagotomized dogs. In the normal dogs occasional reverse peristalsis is seen, while in dogs with vagus nerves sectioned it has not been observed. In sympathectomized animals the augmentation in peristaltic activities which follows the period of inhibition is distinctly less severe than in normal and in vagotomized dogs. Minute doses of pitressin produce only inhibition in the three groups of animals.

With frequent injections of pitressin, lesions of the stomach are obtained in normal and in vagotomized animals. However, ulcerations are obtained in a greater percentage of the vagotomized group, the lesions are more extensive, and acute hemorrhagic duodenitis is also found. In sympathectomized animals gastric lesions are not obtained. In 1 animal a few superficial erosions were seen in the duodenum.

Microscopically, some of the ulcers observed extended down to the muscularis and resembled those seen in man.

In the groups of animals that were vagotomized and sympathectomized but were not given pitressin, no ulcers were found.

The role of vascular alterations (functional and anatomic), particularly in a subject with a constitutional habitus characterized by increased irritability and vasomotor instability, in the genesis of peptic ulcer is emphasized.

737 East Seventy-Ninth Street.

15. Petersen, W. F., and Milliken, M. E.: The Patient and the Weather, Ann. Arbor, Mich., Edwards Brothers, 1935, vol. 2; 1936, vol. 1, pt. 2; 1938, vol. 4, pt. 3.

# VITA

The writer was born in Chicago, Illinois, June 12, 1909, receiving his preliminary education in the Chicago Public Schools. His college work was taken at Crane College in Chicago and Northwestern University in Evanston, Illinois. He matriculated at the University of Illinois, College of Medicine, receiving his B.S. in 1932. He registered in the Graduate School in 1932, receiving his M.S. degree in 1934. In 1935 he obtained his M.D. degree.

Beginning July 1, 1934 he interned for six months at the Kankakee State Hospital and then interned for one year at the Los Angeles County Hospital.

In January 1936 he returned to the University of Illinois, the Department of Pathology, to work under Dr. William F. Petersen, and has also come under the supervision of Dr. D. J. Davis. He has continued his graduate work in pathology up to the present date. In 1938 graduate work was begun by him under Dr. Robert W. Keeton, in the Department of Medicine.

In 1936 he was appointed Assistant in Pathology. In 1937 he was appointed Instructor in Pathology. In 1938 he was also appointed Instructor in Medicine and has retained these positions since that time.

He is a member of Phi Lambda Kappa, and Sigma Xi. He is a member of the Chicago Pathological Society, Chicago and Illinois Medical Societies, and the American Medical Association.

His present hospital associateships are: Associate Medical Staff at the Woodlawn and Englewood Hospitals.

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*Printed and Published in the United States of America*